Polymerizing Phostones: A Fast Way to In-Chain Poly(phosphonate)s with Adjustable Hydrophilicity

Polymerizing phostones: A fast way to in-chain poly(phosphonate)s with adjustable hydrophilicity

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Abstract

Phostones, i.e. 2-alkoxy-2-oxo-1,3-oxaphospholanes, are accessible in a one-pot reaction from commercially available 1,3-dibromopropane and alkyl phosphites. These 5-membered cyclic phosphonic acid esters are used for the preparation of linear poly(phosphonate)s via ring-opening polymerization resulting in polymers with a hydrolytically stable P-C bond in the polymer backbone. Phostones have the stable P-C-bond within the cycle, which leads to a dramatic increase of the monomer stability towards hydrolysis and long shelf-lives compared to other cyclic phosphoesters, which hydrolyze immediately at contact with water. Two phostone-monomers containing ethoxy or butoxy pendant chains were prepared in a single step synthesis from inexpensive starting materials avoiding the usage of $SOCl_2$ or $POCl_3$. Polymers with ethoxy side chains are water-soluble without a lower critical solution temperature, non-toxic to murine macrophages, and hydrolytically degradable under basic conditions. The polymerization kinetics for different catalyst systems were evaluated for both monomers in order to identify optimal polymerization conditions, resulting in polyphosphonates with molecular weights between 3000 and 25100 g/mol with reasonable molecular weight dispersities (<1.6). Due to the ease of synthesis and distinct different hydrolysis kinetics compared to side-chain polyphosphonates, we believe that these new polyphostones represent a valuable addition to water-soluble biopolymers for future biomedical applications.

Keywords: ring-opening polymerization, poly(phosphoester), polyester, phosphate, phosphonate.

Introduction

Phosphorus-containing polymers, and especially poly(phosphoester)s (PPEs), are promising materials for biomedical applications.[1-2] The pentavalent phosphorus atom allows the design of modular structures and the inherent ester bonds in the polymer backbone make them hydrolytically degradable. Furthermore, water-soluble PPEs are promising candidates for drug delivery vehicles,[3-5] due to their "stealth effect", similar to poly(ethylene glycol) (PEG), while their degradability prevents any potential bioaccumulation.[6-7] Through precise control of their chemistry, the physical properties, degradation products, and time can be tuned. [8-10]

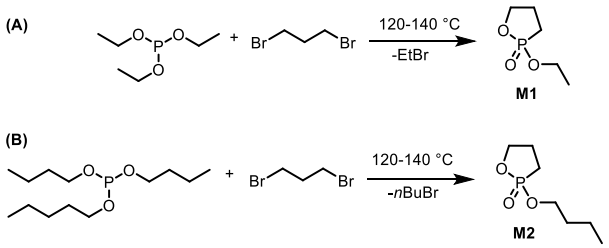
In recent years, we have been studying PPEs and developing both novel synthetic protocols and potential applications. We have focused our efforts on an almost forgotten subclass of PPEs: the poly(phosphonate)s. They contain a chemically stable P−C bond, replacing one of the P−O−C bonds of poly(phosphate)s, which has a strong influence on hydrolysis rates, as the P-C-bond itself is stable against hydrolysis, but microorganisms can cleave the phosphonate linkage.[11] However, poly(phosphonate)s are mainly found as aromatic oligomers prepared by step-growth polymerization and very few water-soluble, well-defined examples have been reported.[12-14] In poly(phosphonate)s the P-C bond is commonly installed as a pendant group, however rare in-chain P-C linkages have been reported.[10, 15-16]

Herein, we report the first ring-opening polymerization (ROP) of 2-alkoxy-2-oxo-1,3-oxaphospholanes with both ethyl and butyl side chains, carrying the P-C-bond within the ring structure and thus forming in-chain poly(phosphonate)s upon polymerization. These so-called phostones have been of some interest in the past, due to their potential application as glycomimetics.[17-19] While the 2-ethoxy-2-oxo-1,3-oxaphospholane heterocycle has been known for a long time,[20-21] it has never been used in ROP to the best of our knowledge. The phostone monomers offer several advantages: The P-C bond in the ring reduces monomer synthesis to a single step from inexpensive, less-toxic starting materials, avoiding $SOCl_2$ and

$POCl_3$. In contrast to other 5-membered cyclic phosphoester monomers, which hydrolyze immediately at contact with water, the phostones are relatively stable towards aqueous hydrolysis and therefore have an extended shelf-life (>12 months) at room temperature, and avoid undue precautions over the presence of water. We report the polymerization of this new class of monomers, exploring different catalysts and monomer: initiator ratios, providing well-controlled and rapid access to PPEs with tunable hydrophilicity and improved hydrolytic stability compared to the analog poly(phosphonate)s with the P-C-bond in the side chain.

Results & Discussion

Monomer synthesis. A preparative route to the target phostones, alkoxy-2-oxo-1,2-oxaphospholanes, was developed. Two monomers with different pendant chains (ethoxy (**M1**) and butoxy (**M2**)) were prepared in order to adjust the hydrophilicity of the resulting polymers. A one-pot reaction of the commercially available 1,3-dibromopropane and the corresponding trialkyl phosphite via consecutive Michaelis-Arbuzov and ring-closing reaction (Scheme 1) avoided the use of the traditional toxic reagents used to prepare other cyclic phosphate or phosphonate monomers.



Scheme 1. One-pot synthesis of monomers **M1** (A) and **M2** (B).

The formation of the phostone monomers from 1,3-dibromopropane and the trialkyl phosphite proceeds in two stages. First, the P-C bond is formed via a Michaelis-Arbuzov reaction accompanied by the elimination of alkyl bromide.[21] The cyclization proceeds within the second

stage via intramolecular nucleophilic substitution and elimination of further alkyl bromide to yield the monomers. Purification is required prior to polymerization, with fractional distillation providing the highest quality, albeit with reduced isolated yields of ca. 20%. The yields are limited because of the presence of side reactions, such as the formation of oligomers by intermolecular nucleophilic substitution reactions or the reaction of the evolving alkyl bromide with the trialkyl phosphite. While further optimization of the synthesis could target improved yields, the focus for this paper was on the polymerization behavior of the phostones so this was not pursued. Purification of the monomers requires two successive distillations, first to remove the oligomeric side product and second a subsequent fractional distillation or column chromatography on the multi-gram scale.

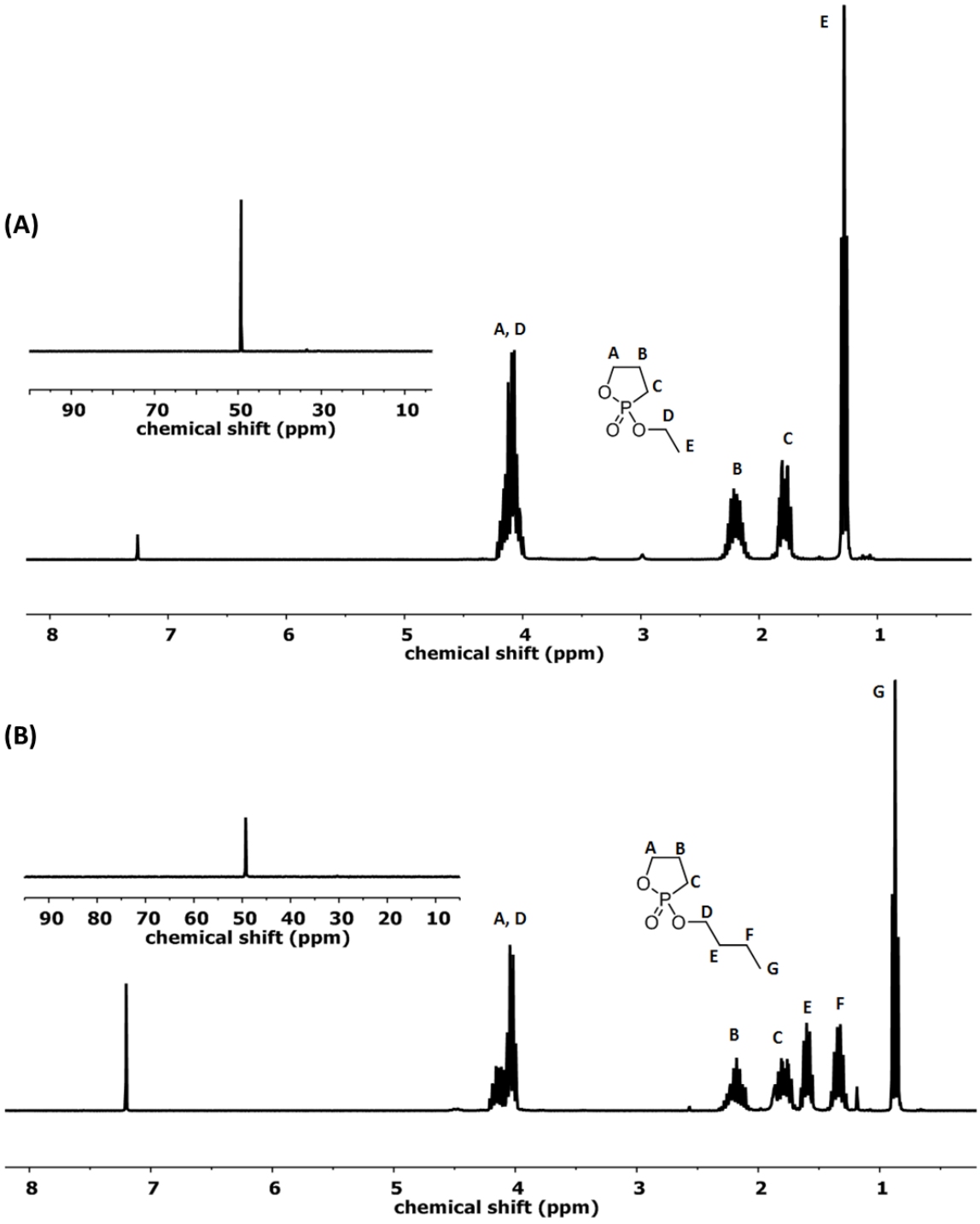


Figure 1. ^{1}H NMRs of (A) **M1** and (B) **M2** ($CDCl_3$, 298 K, 300 MHz); ^{31}P NMRs ($CDCl_3$, 298 K, 121 MHz

The ^{1}H NMR spectra of both compounds exhibit two distinctly separated signals for the cyclic methylene groups B and C (**Figure 1**) typical for the rigid ring structure and complex splitting pattern due to J coupling to the phosphorus atom. The ^{31}P NMR spectra show a single resonance

at 49.24 ppm for **M1** and at 49.28 ppm for **M2**, similar to the resonances of the cyclic phosphonates with the P-C-bond as pendant chain.[10, 16] However, a distinct difference between phostones and the cyclic phosphate (EEP) and phosphonate (EtEPn) was observed concerning their stability. While the cyclic phosphonates with the P-C-bond in the pendant chain as well as the phosphates must be stored under inert gas at low temperatures (-20°C) to avoid degradation or spontaneous polymerization, the phostones show no such tendencies. ^{31}P NMR spectroscopy in deuterium oxide showed immediate ring-opening for the cyclic phosphates and side chain phosphonates by a distinct signal shift to the high field, while the phostone stayed intact upon contact with deuterium oxide at least two days (Figure S30). This increased stability of the phostone monomers can be attributed to a reduced ring-strain compared to the phosphates and side chain phosphonates. Higher ring strain energy is often indicative of a better polymerization in cyclic phosphoesters.[22] The ring strain energy can be evaluated as the difference between the formation enthalpy and the enthalpy of a strain-free model reference compound (see the Supporting Information for calculation details).[23] Here we compare the ring-strain energy of one representative compound of each five-membered monomer class, i.e. the phosphates, phosphonates, and phostones. The six-membered 2-ethoxy-1,3,2-dioxaphosphorinane-2-oxide (**M5**) was used as a reference compound (

).[22]

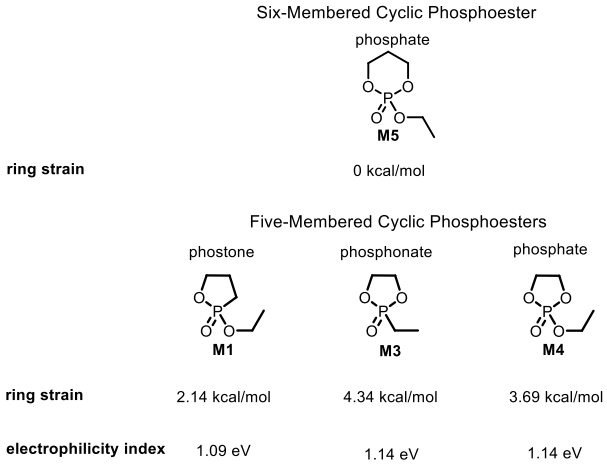


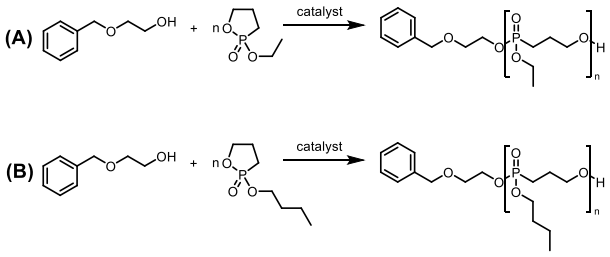
Figure 2. DFT (B3LYP/ functional and aug-cc-pVTZ basis setlevel of theory) calculated calculations of the ring strain energies (kcal /mol−1) and the electrophilicity index (ω+, eV) of six-membered cyclic phosphoester (**M5**) and of five-membered cyclic phostone (**M1**), phosphate (**M3**) and phosphonate (**M4**) heterocycles.

The calculations show significantly a reduced ring-strain energy of 2.14 kcal mol^{-1} for the phostone monomer (**M1**) compared to the phosphate (**M3**) and phosphonate (**M4**) monomer with ring-strain energies of 3.69 and 4.34 kcal mol^{-1}, respectively. The decreased ring-strain energy of **M1** can be rationalized by the replacement of one P-O-bond (162 pm) in the ring structure by a longer P-C-bond (184 pm).[16, 24] Moreover, we have also calculated the electrophilicity index (ω^+) of the monomer **M1**, **M3** and **M4**. The results show that **M1** has a smaller ω^+ than that of **M3** and **M4**. This finding indicates that **M1** has a lower reactivity than other two monomers, which is in good agreement with the experimental observations.

Ring-opening polymerization of phostones. A range of catalysts was investigated for the ROP of alkoxy-2-oxo-1,2-dioxaphospholanes (monomer concentration was set to 2 M in all cases); monomer purity is crucial for efficient ROP. (**Figure** S5). Finally, the Lewis acidic ^{tBu}[salen]AlMe polymerized **M1**, albeit to lower conversions than other systems. While the Al

catalyst was capable of polymerizing monomers at a lower concentrations than the organocatalysts, the resulting ill-defined materials indicated organocatalysts are better suited for these systems, contrasting results for phosphonates where Al salen systems were excellent mediators of ROP.[27]

Table 1 shows that **M1** polymerized readily with 1,5,7-triazabicyclo[4.4.0]undec-7-ene (TBD) as single catalyst in several hours, while the polymerization of **M1** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as single catalyst, which is an effective catalyst for the polymerization of other phosphoester monomers,[25] did not produce any polymer in the case of **M1** under these conditions (after 24 h, at 0°C or room temperature). In contrast, the combination of DBU with urea-derived co-catalysts turned out to be suitable for the polymerization of phostones. The combination of DBU and 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexyl thiourea (TU) as catalyst system[24] was already established for the polymerization of other phosphoester monomers and turned out to be also effective for the polymerization of phostones leading to high monomer conversions above 90% (determined by ^{31}P NMR spectroscopy) within reaction times of up to 5 days.



Scheme 2: Ring-opening polymerization of **M1** (A) and **M2** (B) to main-chain and in-chain polyphosphonates.

As second dual catalyst system DBU combined with 1,1',1"-(nitrilotris(ethane-2,1-diyl))tris(3-(3,5-bis(trifluoromethyl)phenyl)urea) (Tris-Urea) was applied for the polymerization of **M1**. The high efficacy of the Tris-Urea cocatalyst for the ROP of lactones within short reaction times and low transesterification rates was recently reported by Kiesewetter et al. [26] This catalyst system was not used for the polymerization of cyclic phosphoester monomers before. But indeed, the combination of DBU/Tris-Urea turned out to be an effective catalyst system for the polymerization of phostones with high monomer conversions of ca. 90 % and significantly decreased reaction times to ~24 h compared to DBU/TU. Furthermore, tin(II) 2-ethyl hexanoate ($SnOct_2$) was attempted to polymerize **M1**, but led to lower monomer conversions of ca. 69 % and rather ill-defined materials (Figure S5). Finally, the Lewis acidic ^{tBu}[salen]AlMe polymerized **M1**, albeit to lower conversions than other systems. While the Al catalyst was capable of polymerizing monomers at a lower concentrations than the organocatalysts, the resulting ill-defined materials indicated organocatalysts are better suited for these systems, contrasting results for phosphonates where Al salen systems were excellent mediators of ROP.[27]

Table 1: **Overview of polymerization conditions tested for the polymerization of M1.**

#	catalyst	$[M1]_0:[I]_0$	$[M1]_0$: [cat]	solvent	T (°C)	Reaction Time	Conv. (%)
1	$SnOct_2$	50	6	tol.	95	18 h	69
2	DBU	40	5	tol.	0 /r.t.	24 h	0
3	TBD	100	5	tol.	0	4.5 h	87
4	DBU/TU	100	5	tol.	0	5 d	>90
5	DBU/Tris-Urea	100	2	tol.	0	30 h	87

6	Al(Salen)	50	2	tol.	100	18 h	24

For the polymerization with TBD, DBU/TU, or DBU/Tris-Urea (Table 1 entries 3, 4, and 5) detailed kinetic investigations were conducted (Figure 2). For the kinetic studies, monomer conversions, as well as molecular weight and molecular weight distributions at different time points, were determined by removing aliquots from the reaction mixture at defined reaction times and terminating in acidic $CDCl_3$. Due to the stability of the phostones, the acetic acid only terminates the polymerization without hydrolyzing the remaining monomer, making an analysis of monomer conversion (by ^{31}P NMR) and molecular weight distribution (by SEC in DMF) straightforward. During the polymerization, the ^{31}P NMR resonance of the cyclic monomer shifts from 49 ppm to 31 ppm for the linear polymer, allowing a quantification of the amount of polymer and residual monomer (see example for **M1** in Figure **2** (A)). For determination of M_n, the reaction aliquots were purified by precipitation into diethyl ether to remove residual monomer. M_n was calculated via ^1H NMR spectroscopy by comparing the integrals of the initiator with the integrals of the polymer.

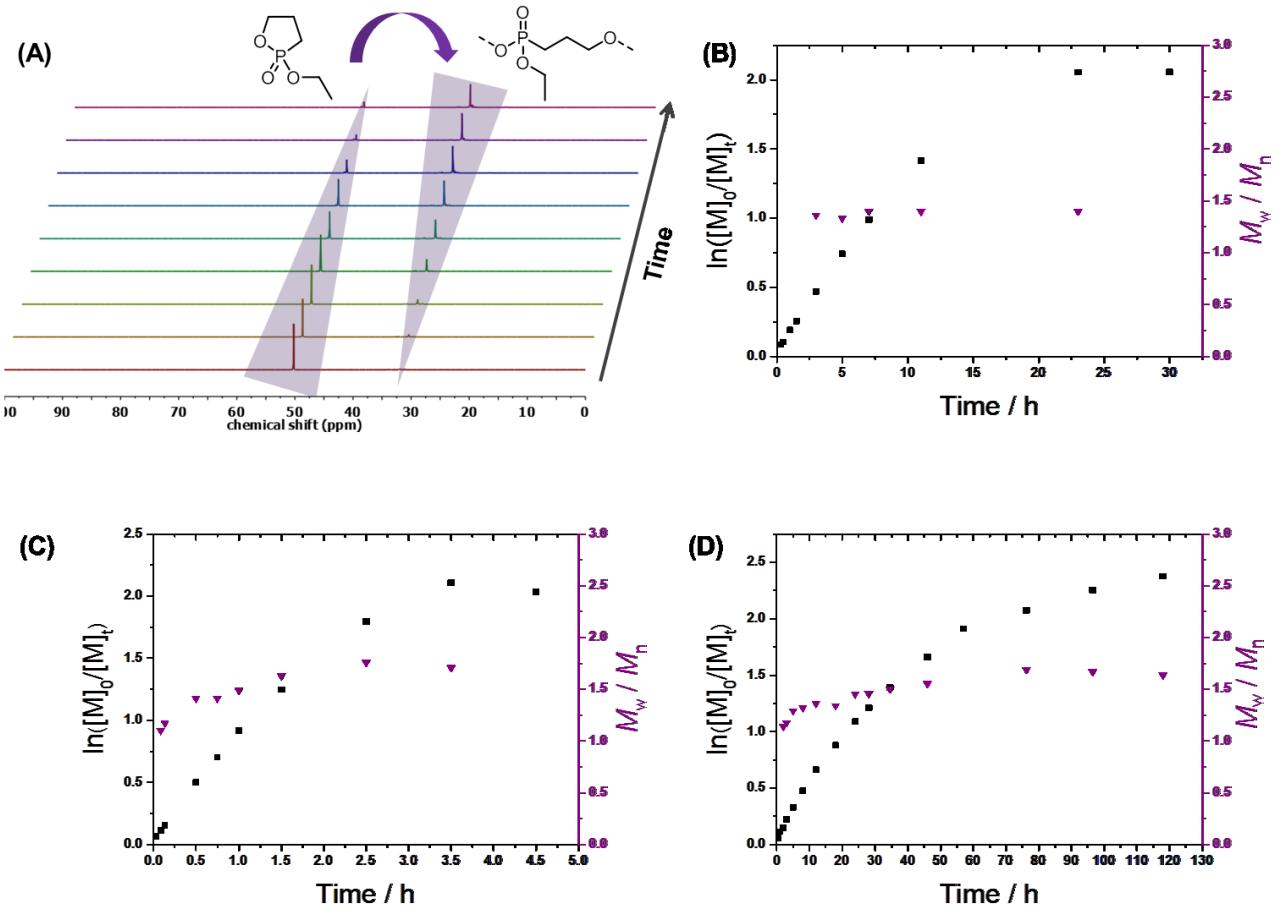


Figure 2. (A) ^{31}P NMR spectra of the polymerization of EPP at different time points. Plots of monomer conversion ($\ln([M]_0/[M]_t)$) *vs* time obtained from ^{31}P NMR spectra for the polymerization of EPP with DBU/Tris-Urea (B), TBD (C) and DBU/TU (D). The ratio of monomer : initiator : catalyst was 100 : 1 : 2 for (A) and 100 : 1 : 5 for (C), (D)

The plots of $\ln([M]_0/[M]_t)$ *vs* time follow first-order kinetics for all catalysts, suggesting a controlled polymerization of **M1**. The polymerization of **M1** with DBU/Tris-Urea proceeds within 24 h with reasonable molecular weight dispersities of $Đ \approx$ 1.3-1.4 (Figure 2 (B)). In contrast, the exchange of Tris-Urea for TU as a cocatalyst leads to a distinct increase of the reaction time from 1 day to 5 days, albeit with similar molecular weight distributions (**Figure 2** (D)). The increased reaction time might be attributed to the lower activity of the TU cocatalyst, previously observed for the ring-opening polymerization of lactones.[26] With TBD as a single dual-functioning catalyst, the polymerization of **M1** was accelerated and final

monomer conversion was reached after 4-5 h (Figure S5). Finally, the Lewis acidic ^{tBu}[salen]AlMe polymerized **M1**, albeit to lower conversions than other systems. While the Al catalyst was capable of polymerizing monomers at a lower concentrations than the organocatalysts, the resulting ill-defined materials indicated organocatalysts are better suited for these systems, contrasting results for phosphonates where Al salen systems were excellent mediators of ROP.[27]

Table 1, Entry 3). However, the high activity of TBD is associated with a broadening of the molecular weight distribution to $Đ \approx 1.7$, probably due to competing transesterification. Reduction of the temperature from r.t. to 0°C or -20°C resulted in decreased propagation kinetics (Figure 3 (A)) and in increased maximum monomer conversion from 86% at room temperature to 93% at -20°C. The change of the temperature also influenced the molecular weight distributions to some extent (1.60 and 1.89), probably due to the increased reaction time of 9.5 h at -20 °C (Figure 3(A)). Figure 3(B) shows the SEC traces for the polymerization of **M1** with TBD at -20 °C. A distinct broadening of the elution peak can be observed from 60 min (corresponding to a conversion of 38%) onwards that can be attributed to transesterification reactions.

The polymerization conditions established for **M1** were transferred to **M2** with similar observations concerning reaction time, monomer conversion, and molecular weight distribution. The polymerization of **M2** at 0 °C with TBD proceeded within ca. 4.5 h to 84% conversion and broad molecular weight distributions of $Đ = 1.5\text{-}2.0$ (Figure S23). The change to Tris-Urea and DBU as catalyst system led to narrower molecular weight distributions of $Đ \approx 1.5$, while the reaction time increased but remained reasonable (36 h, Figure S23**Error! Reference source not found.**). Conversions >90% were achieved with Tris-Urea/DBU.

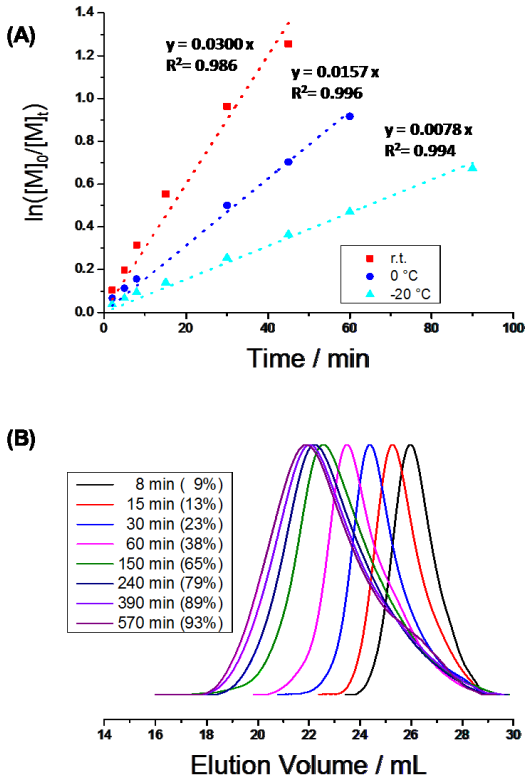


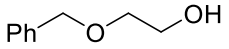
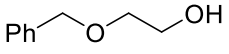
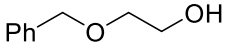
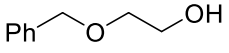
Figure 3. Temperature variation for the polymerization of EPP with TBD as catalyst at r.t., 0 °C, -20 °C. The ratio of monomer : initiator : catalyst was 100 : 1 : 5. (A) Plots of monomer conversion ($\ln([M]_0/[M]_t)$) *vs* time obtained from ^{31}P NMR spectra. (B) SEC traces for the polymerization of **M1** with TBD at -20 °C with Đ=1.89.

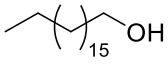
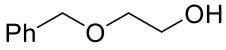
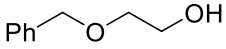
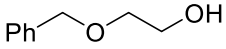
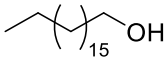
Polymers P(1) and P(2) are readily soluble in common organic solvents such as THF, DCM or $CDCl_3$, while P(1) is water-soluble up to concentrations of at least 10 mg mL^{-1}. Like the corresponding polyphosphate (PEEP) and side-chain polyphosphonate (P(3)), P(1) shows no macroscopic phase separation from aqueous solution, even at high concentrations of 10 mg mL^{-1} in milliQ water or PBS. However, turbidity measurements of P(1) in water showed a slight but constant transmission drop during the measurement, until a transmission of roughly 90% is reached, while for the 'naked eye' the polymer solution remained transparent (Figure S18(a)). Temperature-dependent dynamic light scattering measurements of the aqueous solution of P(1)-4 (c=5 mg mL^{-1} in water) showed the formation of temperature independent

aggregates with hydrodynamic radii R_h of ca. 120 nm (Figure S18(b)). In contrast, DLS measurements of the corresponding side-chain-phosphonate P(3) (M_n=6000 g mol^{-1}, DP=50 (Figure S19)) only exhibited molecularly dissolved polymer with R_h=2 nm (Figure S19) and no aggregates at least up to 10 mg mL^{-1}. Solution properties of water-soluble PPEs are currently a focus of deeper investigation for our group.

Thermal Properties. All PPEs synthesized in this study are colorless, viscous, honey-like materials with low glass transition temperatures from -48 to -58°C for P(1) and -60 to -65°C for P(2). Such values are comparable to other aliphatic PPEs prepared by ROP (Table 2).[10] Thermal gravimetric analysis shows a single mass loss starting at T_{on} between 260-300°C, which is again comparable to structural similar poly(phosphate)s (Figure S14 and S15).

Table 2. Polymer properties of P(1) and P(2) prepared by ring-opening polymerization

Entry	initiator	catalyst	DPn_{theo}	DPn^a	M_n / gmol^{-1} ^{a}	T_g / °C^b	M_w/M_n ^{c}
P(1)-1		TU/DBU	20	19	3000	-48	1.25
P(1)-2		TU/DBU	50	49	7500	n.d.	1.47
P(1)-3		TU/DBU	60	54	8300	-56	1.24
P(1)-4		TU/Tris-Urea	170	166	25100	-58	1.56

P(1)-5		TU/DBU	40	40	6300	-50	1.50
P(2)-1		TBD	20	21	3900	-65	1.56
P(2)-2		TBD	50	47	8500	-64	1.61
P(2)-3		TBD	100	73	12800	-60	1.55
P(3)-1		DBU	40	40	5900	-46	1.10

[a]Determined via 1 H NMR. [b]Determined by differential scanning calorimetry. [c]Determined via SEC in DMF.

Toxicity. PPEs are currently regarded as promising materials for biomedical applications. However, phosphorus-containing compounds and especially phosphonates with good leaving groups attached to phosphorus gained notoriety, due to their application as chemical warfare agents. Many phosphonates are known to inhibit acetylcholinesterase (AChE) irreversibly, which is the typical mode of action of nerve agents.[28] AChE is an enzyme that hydrolyzes the neurotransmitter acetylcholine (ACh), terminating incoming nervous signals and serving as a regulator of neurotransmission by ACh hydrolysis. Irreversible inhibition of AChE results in accumulation of acetylcholine in cholinergic receptors and continuous stimulation of the nerve fiber leading to, among other symptoms, bronchospasm and respiratory failure.[29] As the phostones hydrolyze slowly in water, the effect of both monomers **M1** and **M2** on AChE was

investigated and no significant influence on the AChE activity up to concentrations of 0.4 g L^{-1} was found. The positive control, tacrine, led to almost complete AChE inhibition even at the lowest concentration of 25 mg L^{-1}. In addition, the cytotoxicity of **M1** and **M2** and the water-soluble polymers P(1) with different degrees of polymerization were evaluated *in vitro* against murine macrophages (RAW264.7). Concentrations ranging from 37.5 to 1000 μg mL^{-1} after 48 h of incubation at 37 °C in Dulbecco's modified eagle medium (DMEM), supplemented with 10% FBS were investigated (Figure 4**,** 20 % DMSO was used as positive control.). Cell viability was monitored as a function of ATP concentration, which was dependent on the number of living cells. **M1** and P(1) showed no toxicity to murine macrophages even at high concentrations, while **M2** shows a slight and dose-dependent cytotoxicity under these conditions (Figure 4 B&C).

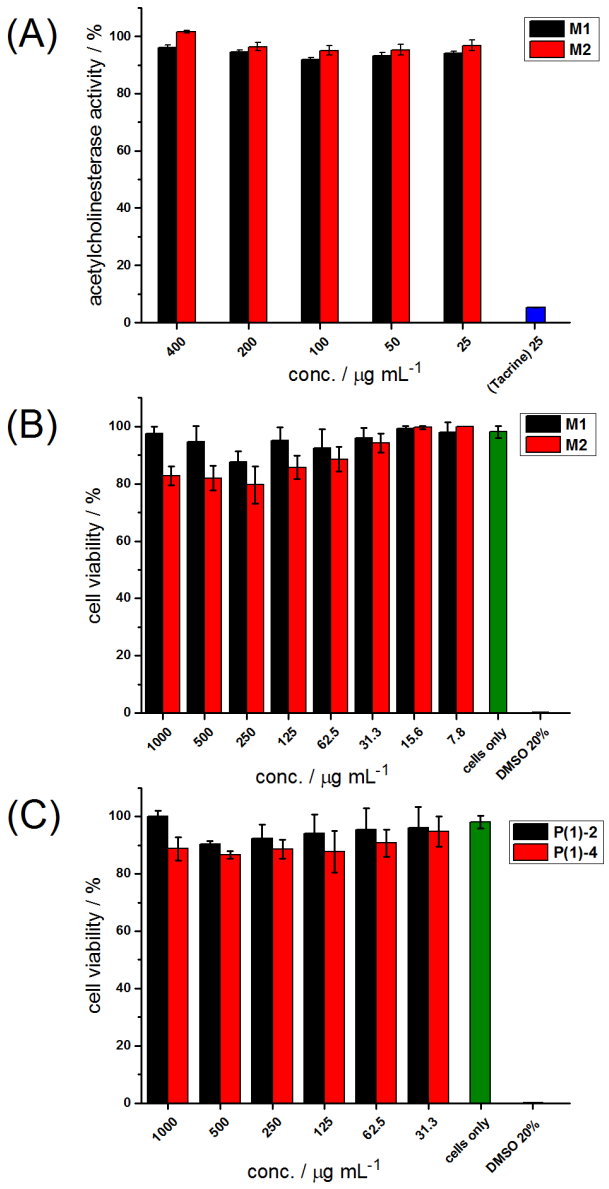


Figure 4.(A) Acetylcholinesterase assay of M1 and M2 with tacrine as positive control (B) *In vitro* cell-viability of murine macrophages (RAW264.7) treated with P(1)-2 and P(1)-4 after 48 h of incubation. The experiments were carried out as triplicates.

Degradation. The location of the hydrolysis-stable P-C-linkage in the PPE backbone was expected to influence the hydrolytic degradation of P(1) compared to other structurally similar PPEs (P(3) and P(4)). In general, degradation of PPEs follows different mechanisms under acidic or basic conditions. In acidic media, the phosphoryl bond is activated by protonation allowing nucleophilic attack of water on the α-carbon atoms.[30] As the α-carbons in the pendant

chains are more accessible, the pendant chains are cleaved faster than the polymer backbone. Under acidic conditions, no or slow degradation has been reported for most PPEs.[30] In contrast, under basic conditions, the degradation of PPEs is induced by nucleophilic attack of hydroxyl anions on the central phosphorus atom leading to a trigonal bipyramidal geometry, wherein the axial position is preferably cleaved. Due to the pseudo rotation of phosphorus, the main chain, as well as the pendant chain, can occupy this position and are therefore cleaved with approximately same rates (for low molecular weight compounds).[30-31]

The degradation of polymer P(1) was investigated at three different pH values (pH 1, 10, 12) and the degradation at pH 10 was compared to the side-chain analog P(3)-1 (**Figure 5** (B)). For polymers P(1) at pH 10 and 12, the degradation proceeded in two phases. In the first phase, a fast degradation was observed, which slows down and reaches a plateau with different degrees of degradation within the second phase. The degradation of P(1) can be accelerated with increasing pH. While the degradation at pH 10 proceeded slowly and did not exceed 10%, even after 10 days, a significant acceleration was observed at pH 12. After 5 days, degradation of ca. 35%, and after 12 days of 40% was observed. The cleavage of the pendant chain was confirmed by the appearance of ethanol signals in the ^{1}H NMR spectra (Figure 5 (C) signals at 1.06 and 3.53 ppm), whereas cleavage of the main-chain is indicated by the evolution of resonances at 3.79 and 1.14 ppm (Figure 5).

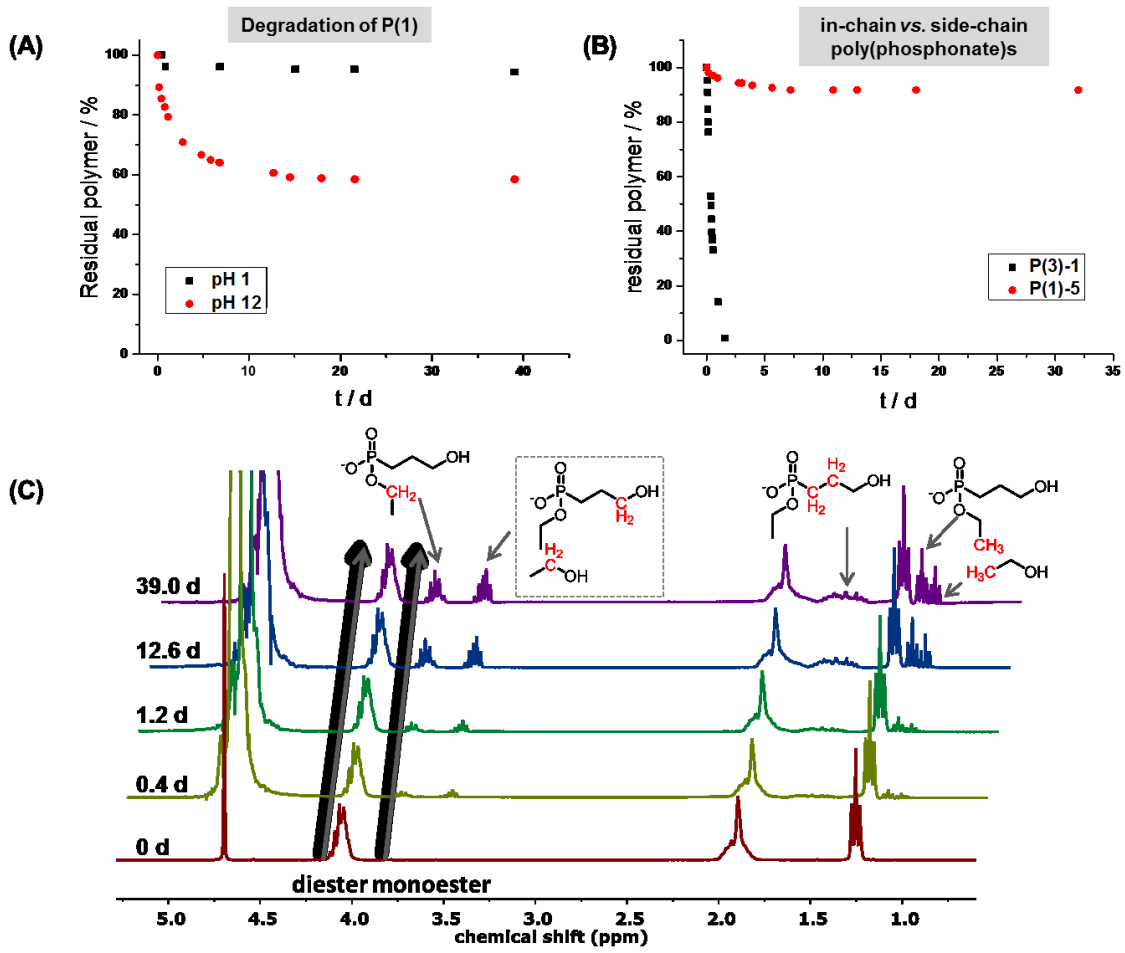


Figure 5. (A) Degradation of polymer P(1) pH 1 (0.1 M HCl containing 10% D_2O) and at pH 12 (0.01 M KOH containing 10% D_2O) . (B) Degradation of P(1) compared to the analog side-chain phosphonate P(3) at pH 10 (borate buffer containing 10% D_2O) (C) ^1H NMR spectra (300 MHz, H_2O/ D_2O 9:1, 298K) of the degradation of P(1)-4 at pH12.

Under acidic conditions (pH 1), only 4% degradation was observed over a period of 40 d. The dramatically decelerated degradation of **P(1)** observed under acidic conditions is in good agreement with the previously reported degradation studies of poly(phosphate)s and side-chain poly(phosphonate)s.[16, 30] In contrast to P(1), the side-chain poly(phosphonate) degraded at pH 10 within two days completely leading to selective degradation and only one break down product, 2-hydroxyethyl phosphonic acid, as confirmed by ^1H NMR spectroscopy. The

dramatic different degradation behavior of the two poly(phosphonate)s may be attributed to their different behavior in water. While polymers P(1) aggregate in water, as described above, the side-chain polyphosphonate P(3) are molecularly dissolved under these conditions (Figure S19). The aggregate formation probably leads to a shielding of the polymer from nucleophilic attacks of the hydroxyl anions thus leading to increased stability compared to P(3). However, this unique degradation behavior of different PPEs is currently under further detailed investigation.

Summary

In summary, we report the first in-chain poly(phosphonate)s prepared by ring-opening polymerization. In contrast to previously reported phosphate and phosphonate monomers, the unique phostone-monomers were prepared by a single-step protocol from inexpensive phosphites and dibromopropane, avoiding toxic reagents. Due to a significantly lower ring-strain of the phostones compared to the phosphate or phosphonate analogs they can be stored at room temperature and show significantly improved resistance to degradation by water. The phostones are thus a powerful alternative to other water-soluble PPEs due to easy monomer handling. However, monomer purification is still crucial to efficient polymerization. Both hydrophilic and hydrophobic materials are accessible by variation of the pendant chains. The controlled nature of the polymerization was shown in detailed kinetic studies with different catalyst systems and different monomer to initiator ratios. The Tris-Urea/DBU catalyst combination was preferred, with significantly reduced reaction times of 24 h and molecular weight dispersities of ca. 1.1-1.6.

Initial studies on the biocompatibility were carried out by treating macrophages with various concentrations of the hydrophilic polymer P(1) and cell viabilities of above 88% were observed

for polymer concentrations up to 1 g/L. The degradation of the hydrophilic polymer in aqueous media was investigated at different pH values and was found to be significantly slower than the degradation of the corresponding side-chain phosphonate, proving that a slight structural difference can lead to different polymer properties. In all, these new polymers offer an intriguing complement to other phosphorus monomers thanks to their ease of monomer synthesis, tunable hydrophilicity, biocompatibility and unique degradation behavior.

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The author declares no competing financial interest.

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